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The following is taken from the documents filed by Applicant

[54] Combinatorial method for preparing and characterizing crystalline and amorphous materials libraries at microgram scale.

[57] The present invention relates to a method for the wet chemical preparation of materials libraries consisting of a plurality of solids wherein the solids are deposited from reaction mixtures in micro-reaction chambers onto a bottom plate, which simultaneously serves as a library substrate. According to the choice of the materials for the library substrate, the solids can be non-destructively examined, for example by reflective a penetrating microarea X-ray diffraction.

Description

The present invention relates to a method for the wet chemical preparation of material libraries consisting of a plurality of solids, wherein the solids are deposited from reaction mixtures in micro-reaction chambers onto a bottom plate, which on the same time serves as the library substrate. The narrowest bottleneck in the development of new active substances, polymers and materials is the discovery of suitable new leading structures. Combinatorial chemistry has established itself as an important tool for the development of new compounds within a few years in the fields of organic, biochemical and pharmaceutical chemistry (e.g., Special issue: Combinatorial Chemistry, *Acc. Chem. Res.*, 1996 29; G. Lowe, *Chemical Society Reviews*, 1995, 24 (5), 309; S.R. Wilson, A.W. Czarmik, *Combinatorial Chemistry – Synthesis and Application*, John Wiley & Sons, 1997). In contrast, in the fields of inorganic solid state synthesis, material research or technical catalysis development, only few examples are known where combinatorial search for materials has been used. The preparation of materials libraries, using a combinatorial materials search has been reported for finding new superconducting materials (X.-G. Xiang et al, *Science* 1995, 268,1738), new magnetoresistant materials (G. Briceno et al., *Science* 1995, 270, 273) and new luminescent materials (E. Danielson et al., *Science* 1998,279,837). All these methods have in common that substances are applied as thin films via electron beam vaporization or RF sputtering under reduced pressure for forming a materials library. The configuration is created by a physical mask, which already resulted in libraries of as much as 25000 materials. The first combinatorial preparation of a materials library by a wet chemical method using ink jet technology led to the development of luminescent materials (D. Sun et al.; *Adv. Mater.* 9, 1046-1049, 1997). A disadvantage of this method is that it can only be employed at normal pressure and low temperatures.

Many of the materials known to date – in particular porous materials important to catalysis can only be prepared by a wet chemical method – often by a hydrothermal process (e.g., M.W. Anderson et al.; *Angew. Chem.*; 1995, 107, 1115; D.P. Serrano et al., *Microporous Materials*, 4 (1995), 273). These methods only differ by the selected ranges of temperature and pressure, the variation of the stoichiometric proportions of the selected precursors and the template molecules selected (L.D. Rollmann, *Inorganic Compounds with unusual Properties-II*, 1979, 387). The synthesis under hydrothermal conditions takes from two hours to several weeks, depending on sample volume and experimental procedure. This is to be followed up

by working-up procedures and product characterization. The most important analytical method is powder diffraction for elucidating the phase structure. Of particular importance to the application of such materials in fields such as catalysis or sensor technology is their pore architecture, which can be controlled in hydrothermal synthesis by the addition of template molecules. Due to the high expenditure of time for one synthesis and the wide variety of possible mixed oxides and template molecules, a systematic and exhaustive examination of the classes of materials has been impossible. Due to the great number of possible polynary mixtures of oxide materials and generally possible template molecules for controlling the pore architecture of such materials, the transfer of the methods of combinatorial chemistry to hydrothermal synthesis is attractive.

The first application of combinatorial methods in hydrothermal synthesis was reported by Akporiaye, Karlson and Wendelbo (D. E. Akporiaye, I. M. Dahl, A. Karlsson, R. Wendelbo, *Angew. Chem.*, 1998, 110, Nr. 5, 629; D. E. Akporiaye, I. M. Dahl, A. Karlsson, R. Wendelbo, patent pending, Norwegian Application No. 97.0788). They developed an autoclave by means of which 100 hydrothermal syntheses (reaction volumes of 500 ml each) at temperatures of up to 200° C can be performed simultaneously. A drawback of this method is that no materials libraries are produced, instead, the solids produced have to be removed from the individual mini-reactors and have to be characterized independently by standard methods. The handling of the samples after synthesis has turned out to be very cumbersome and limits the performance of this combinatorial approach. We have now found that materials libraries can be prepared by wet chemical methods using extremely low quantities of materials (reaction volumes of 2 μ L or less). A great number of reaction mixtures of various compositions are simultaneously reacted in micro reaction chambers included in a plate ("reaction plate"), e.g. in the form of bores; the solids produced being deposited on the bottom plate of the reactor. Subsequently, the solids are freed from the supernatant liquid phase and are calcined whereby they adhere in a spatially separated way to the bottom plate. By appropriately selecting the material of the reactor bottom plate of the reactor, it may also serve as the library substrate. Alternatively, the solids or subsets thereof may be transferred to a plastic sheet provided with an adhesive layer so that a printed materials library on another library substrate is formed. Depending on the material selected for the reactor bottom plate or the sheet, respectively, different analytical methods can be employed for characterizing the solids, such as reflecting microarea X-ray diffraction if the bottom plate is made of a material which scatters

X-rays elastically and causes low background noise. Suitable materials include single-crystal wafers, preferably of Si, Cu, quartz, rutile, anatase, zirconia, Ge, Al, sapphire, Fe, Te, Zr, Co, Ni, or, Sn, more preferably a (711) Si- single-crystal wafer. Materials suitable for analysis with penetrating micro area X-ray diffraction are X-ray transparent for example kapton, kevlar, teflon, mylar, PVC, polyethylene, polypropylene, polycarbonate, Al, Be or Mg in a layer thickness of $<100\text{ }\mu\text{m}$, preferably $<10\text{ }\mu\text{m}$. The reactor for generating the materials libraries has a layered structure: over the reactor bottom plate which may serve as the library substrate, there are provided at least 2 reaction plates of an inert material having bores of from 0,05-20 mm in diameter, which serve as micro reaction chambers. The topmost reaction plate consists of a hard material, for example steel. On top thereof, there is a sealing layer without bores, e.g., made of teflon above which there is another layer of a hard material with which the reactor layers are compressed and sealed by suitable devices. When the materials employed are appropriately selected, reacting temperatures of up to 1000°C are possible; when teflon is used for sealing a maximum of 350°C is possible. The reactor can have very small dimensions and extremely small reactor volumes and meets the highest safety demands. A reasonable and practicable miniaturization of the materials library is currently limited only, on the one hand, by the focusability of the X-ray beam during the measurement of X-ray diffraction, and on the other hand, by the dimensions of the liquid dispensing means. While 10 samples can already be analysed with an X-ray beam having a diameter of $50\text{ }\mu\text{m}$ ($10,000\text{ samples / cm}^2$), only 5 samples per mm [in a mini reactor height of 10 mm] can be realized for a dispensible sample quantity of $0.5\text{ }\mu\text{L}$ height ($= 2,500\text{ samples / cm}^2 = 2,500,00\text{ samples - dm}^2$).

By applying combinatorial techniques to synthesis optimizations, systematic variations of the compositions and preparation conditions enables a fast optimization of solid syntheses and a drastic speed-up of the discovery of new solids. The development of materials can be performed in a normal laboratory without additional safety measures and at low costs. Due to its small dimensions, the reactor can be handled without problems in glove boxes under inert gas, and when appropriately modified, it can be charged with reactive gases such as ammonia, chlorine, methane, borane, HCl, hydrogen, oxygen or fluorine, it can be hermetically sealed and can be thus employed for the synthesis of new materials.

An automated examination of all solids of a thus prepared materials library is possible, for example by using the phase identification of the individual materials by means of a commercial GADDS-micro diffractometer of Bruker-AXS (M. Schuster, H. Göbel, Appl. Phys. 28 (1995) A 270 - A275; H. Göbel, PCT Int. Appl. WO 95/22758 A1). This concept enables a direct identification of the substances formed. The separate preparation of samples for measurement is avoided. In addition to phase identification by non-destructive micro area X-ray diffraction, the complete library can be used for other examinations such as catalytic activity using IR-thermography (Maier, Holzwarth, DE-A19757754.7 of December 23, 1997) luminescence, magnetic resistance and other characterizations.

In particular the method relates to the preparation or deposition of crystalline and amorphous solids from liquid phases such as solutions, emulsion, suspension or sols. Above all, suitable fields include sol gel synthesis (C.J. Brinker, G.W. Scherrer " Sol-Gel-Science, the Physics and Chemistry of the Sol-Gel-Process", Academic Press, New York 1990), hydrothermal synthesis (Kiek-Othmer (3rd) 6,321), hydro metallurgy, decomposition of preceramic materials to produce hard materials (D. Segal, Chemical Synthesis of Advanced Ceramic Materials, Cambridge University Press, New York 1989) and polymerizations. The methods according to the invention are useful, for example, for the discovery of new materials in the field of inorganic solids, in particular, in the field of mixed-oxides, mixed-carbides, mixed-nitrides and mixed-borides. These materials are employed in many fields of everyday life and industrial production as lead-structures for catalysts, optical wave guides, coatings, semiconductors, super-conductors, ferro magnetic materials, magnetic resistors, optical materials, hard materials, luminescent and fluorescent materials, sensors, NLO-materials and special materials and many more. Especially, the class of substances of crystalline including porous materials such as zeolites or amorphous porous mixed-oxides, mixed-carbides or mixed-nitrides is of great interest to the industry. They are employed as catalysts for oil refinement in petrochemistry as well as for the preparation of pharmaceuticals fine and bulk chemicals. A wide variety of oxidation reactions is catalyzed by them: aromatic hydroxylation, olefin epoxidation, ketone ammoxidation, alcohol oxidation and alkane-oxy-functionalization to name but a few. Similarly promising are the stable amorphous mixed-oxides whose properties are as important as those of the crystalline materials but whose preparation is mostly simpler than that of well-defined crystalline materials.

Example

The combinatorial modification of a conventional, laboratory titanium sylicalite synthesis under hydrothermal conditions (UK-patent 2071071B) is used as an example to show how a materials library of crystalline and amorphous material can be prepared and analyzed with a minimum expenditure of time.

The reactor employed:

Figure 1 shows a construction drawing of a pressure tight reactor. In a cylindrical pressure vessel made of steel (total diameter: 40 mm, inner diameter: 24.5 mm) having a height of 22,7 mm , there is provided a Si single-crystal wafer of 22 mm diameter. By three screws, a steel plate with a Teflon insert is pressed on to this Si single-crystal wafer with bores in the plate representing the reaction chambers.

Figure 2 shows the pattern with the corresponding distances. The different reaction solutions are pipetted in to this mask by means of a robot or by hands (1 to 2 μ L). A further Teflon disk follows – as a seal for the reaction and which is again pressed against the remaining structure using a thick steel plate and three screws so that the whole assembly is pressure-sealed.

Experimental sample:

In a typical charge 2.27 g (10.9 mmol) of tetraethyl orthosilicate (TEOS) is mixed with 75 mg (0.33 mmol) tetraethyl titanate in a 10 ml vessel. 4 g (5 mmol) of a 25% by weight solution of tetrapropylammoniumhydroxide is added to this solution and stirring is continued for 1 hour. After 5-6 hours of heating to 80 - 90° C, the resulting alcohol is completely evaporated. Distilled water is added to the solutions to make 7.5 ml, and a typical reaction solution is obtained. 37 combinatorial modification of that experimental charge were prepared according to the information given in table 1.

<Table 1>

Table 1: Composition of the material points of the library in figure 2.

"Mixture" indicates the molar ratio of the metal oxides employed (and thus the oxide materials in the forming product) to the template molecule employed. Tetraethoxysilane ($\text{Si}(\text{OEt})_4$, TEOS), $\text{Ti}(\text{OEt})_4$, $\text{Ti}(\text{O}^i\text{Pr})_4$ or $\text{Ti}(\text{O}^n\text{Pr})_4$, $\text{Zr}(\text{O}^n\text{Pr})_4$ and $\text{Al}(\text{O}^{\text{sec}}\text{Bu})_3$ were employed as sources for SiO_2 , TiO_2 , ZrO_2 and Al_2O_3 . Since distilled water was added to the externally prepared samples to make 7.5 ml after evaporation of the alcohols an excess of water of water:metal of 40:1 is present for the hydrothermal synthesis in all samples.

A1 and F1 contain each the described above original charge. Bores A1-G3 (Fig. 2) are filled with 1 to 2 μL of the charges from table 1. "Mixture" represents the molar ratio of the employed metal alkoxides (and thus the oxide materials in the forming product) to template molecules employed. Since distilled water was added to the externally prepared samples to make 7.5 ml after evaporation of the alcohols an excess of water of water:metal of 40:1 is present for the hydrothermal synthesis in all samples. The reaction was carried out with the closed reactor at a temperature of 200 °C over a period of 36 h.

Post treatment of the materials library:

The reaction is followed by lifting the top steel and teflon plates, and the products in the micro-reaction chambers are separated from the mother liquor by removing the supernatant liquid using conventional techniques such as porous magnesia sticks. Ideally, this is carried out using appropriate tools in one working step. Subsequently, the substances are repeatedly washed with 2 μL of distilled water. Thereafter, the open reactor with the products can be dried and when teflon is used as the reactor plate, calcined at a maximum of 350° C, preferably 130° C, which results in a good adhesion of the solids formed to the reactor bottom plate. After removing the two reaction plates of steel and the teflon insert the thus produced materials library (original bottom plate) can be further treated or examined. In case of the zeolite synthesis as sought here, the materials library was tempered in an oven at 600 °C for 10 hours. If the products are to be analyzed in a vertical position the adhesion of the samples can be improved by a spraying a suitable amorphous varnish onto the library. The varnish can subsequently be removed by evaporation or oxidatively removed at elevated temperatures.

Identification of the solids:

The identification of the phases of the products formed was effected with a GADDS-micro area X-ray diffractometer with a Göbel mirror and a HI/STAR-detector. The Si plate was attached to a xyz-sample table and subsequently, after inserting the scanning parameters and recording of the spots to be measured its reflection was measured in a fully automated way. The powder diffractograms were recorded with a 500 μm collimator integrally over the whole "spot" area. By using a tilted Göbel mirror focussing of the X-ray beam to as narrow as 50 μm with a high X-ray intensity is possible. Thus, individual particles in the micrometer scale of X-ray analytical examination are accessible. Under these measuring conditions, no reflection from the Si sample holder are found. By using a thin foil as reactor bottom or by transferring the library onto a thin foil having an adhesive layer a diffractogram can be also be recorded in the transmission modus. The diffractograms obtain are conveniently recorded for later evaluation and can be identified by hand or in a fully automated way using standard libraries for comparison.

The evaluation of the diffractograms showed that the spots highlighted in gray in figure 2 contain crystalline fractions while all non-highlighted spots contain amorphous material. The structure of the crystalline phases was identified by comparison of their diffractograms with a diffractogram library. The reaction mixtures for producing the solids in spots A1 and F1 correspond to the classic synthesis. In figure 3, the powder diffractogram from the conventionally prepared zeolite (top) is compared with diffractogram of points A1 and F1. This figure shows that the microgram quantities of the materials produced in the materials library are identical with that obtained by a conventional synthesis.

Fig. 1 is a special embodiment of a reactor as employed in the example.

Fig. 2. Identification of the materials library. The composition of the individual sample points are summarized in table one.

Fig. 3. This figure shows at the top an example of an X-ray diffractogram of a conventionally prepared TS-1-zeolite and below the identical X-ray diffractogram obtained by the materials library at the indicated spots of substance quantities in the μg -area. This proves that crystalline inorganic materials such as zeolites can be prepared and identified according to the methods described herein.

Claims

1. A method for the wet chemical preparation of a materials library comprising a plurality of solids from reaction mixtures having various compositions, **characterized in that** the reaction mixtures are introduced in a spatially separated way in microreaction chambers in removable reaction plates into a reactor and reacted, and wherein the solids produced in the reactions being deposited, in a spatially separated way on a removable reactor plate.
2. A method according to claim 1 wherein the reaction mixtures are reacted in form of solutions or suspensions in micro-reaction chambers being isolated cavities present on the reactor plate in the form of bores at temperatures of up to 100 °C and internal pressures of up to 1000 bar.
3. A method according to claim 1 wherein subsequently the solids deposited on the reactor bottom plate are freed from the supernatant liquid phase and calcined
4. A method according to claim 1 to 3 wherein the reactor bottom plate, which consists of a material that elastically scatters X-rays is identical with the library substrate onto which the solids are deposited adhesively and together with the deposited solids forms the materials library.
5. A method according to claims 1 to 3 wherein a subset of all deposited solids is subsequently transferred to a foil provided with an adhesive layer. Said foil being made of an X-ray transparent material, and which forms the substrate for the materials library together with the solids transferred thereto.
6. A method according to claim 1 to 5 wherein the solids of the materials library are subsequently characterized by non-destructive analytical methods.
7. A method according to claim 4 wherein the reactor bottom plate consists of a single-crystal slice preferably consisting of Si, Cu, quartz, rutile, anatase, zirconia, Ge, Al, sapphire, Fe, Ti, Zr, Co, Ni or Sn.

8. A method according to claim 7 wherein the reactor bottom plate comprises a (711) Si-single crystal wafer.
9. A method according to claim 4 wherein the reflective microarea X-ray diffraction is employed as analytical method.
10. A method according to claim 5 wherein penetrating microarea X-ray diffraction is employed as analytical method.
11. A method according to claim 5 wherein kapton, kevlar, teflon, mylar, PVC, polyethylene, polypropylene, polycarbonate, Al, Be or Mg in a layer thickness of $\leq 100 \mu\text{m}$ is employed as X-ray transparent material.
12. A method according to claim 11 wherein the layer thickness is less than $10 \mu\text{m}$.
13. A method according to claim 1 wherein the reactor has a layered structure essentially comprising: a reactor bottom plate, on top thereof a lower part of a reaction plate made of inert materials, having bores of 0.05 - 20 mm in diameter, on top thereof an upper part of a reaction plate made of a hard material having identical bores, on top thereof a sealing layer, on top thereof a layer of hard material with which the reactor layers are compressed and sealed using suitable devices.
14. A method according to claim 13 wherein the inert material consists of kapton, teflon, graphite, kevlar, mylar, or steel.

In the following 3 pages of figures.

Table 1: Composition of the Material Spots in the Library of Fig. 2.

Bore	Mixture	Bore	Mixture
A1	Si : Ti : NPr ₄ OH 1 : 0.03 : 0.45	D5	Al : Ti : CTAB 1 : 0.05 : 0.1
A2	Si : Ti : NBu ₄ OH 1 : 0.03 : 0.45	D6	Al : Zr : NBu ₄ OH 1 : 0.2 : 0.4
A3	Si : Ti : NEt ₄ OH 1 : 0.03 : 0.45	D7	Al : Zr : NMe ₄ OH 1 : 0.2 : 0.4
B1	Si : Ti : NMe ₄ : OH 1 : 0.03 : 0.45	E1	Al : Zr : NEt ₄ OH 1 : 0.2 : 1
B2	Si : Ti : C ₄ H ₉ N 1 : 0.03 : 0.45	E2	Al : Zr : CTAB 1 : 0.2 : 0.1
B3	Si : Ti : CTAB 1 : 0.03 : 0.045	E3	Ti : Zr : NBu ₄ OH 1 : 1 : 0.4
B4	Si : Ti : hexadecylamine 1 : 0.03 : 0.045	E4	Ti : Zr : NBu ₄ OH 1 : 1 : 0.4
B5	Si : Ti : hexadecylamine : NaOH 1 : 0.03 : 0.045 : 0.45	E5	Ti : Zr : NMe ₄ OH 1 : 1 : 0.4
C1	Si : Al : NPr ₄ OH 1 : 0.033 : 0.43	E6	Ti : Zr : NEt ₄ OH 1 : 1 : 1
C2	Si : Al : NPr ₄ OH 1 : 0.066 : 0.43	E7	Ti : Zr : CTAB 1 : 1 : 0.1
C3	Si : Zr : NPr ₄ OH 1 : 0.03 : 0.98	F1	Si : Tu : NPr ₄ OH 1 : 0.03 : 0.45
C4	Si : V : NPr ₄ OH 1 : 0.03 : 0.45	F2	Si : V : NPr ₄ OH 1 : 0.03 : 0.45
C5	Si : Zr : NBu ₄ OH 1 : 0.03 : 0.4	F3	Si : Ti : NEt ₄ OH 1 : 0.03 : 0.45
C6	Si : Zr : NMe ₄ OH 1 : 0.03 : 0.4	F4	Si : Zr : NPr ₄ OH 1 : 0.01 : 0.98
C7	Al : Ti : NBu ₄ OH 1 : 0.05 : 0.4	F5	Si : Al : NPr ₄ OH 1 : 0.1 : 0.43
D1	Al : Ti : NMe ₄ OH 1 : 0.05 : 0.4	G1	Si : Ti : NPr ₄ OH 1 : 0.03 : 0.45
D2	Al : Ti : NEt ₄ OH 1 : 0.05 : 1	G2	Al : Si : NPr ₄ OH 1 : 0.2 : 0.43
D3	Al : Ti : NEt ₄ OH 1 : 0.05 : 1	G3	Al : Si : NPr ₄ OH 1 : 0.1 : 0.43
D4	Al : Ti : CTAB 1 : 0.05 : 0.1		

(figures page 1)

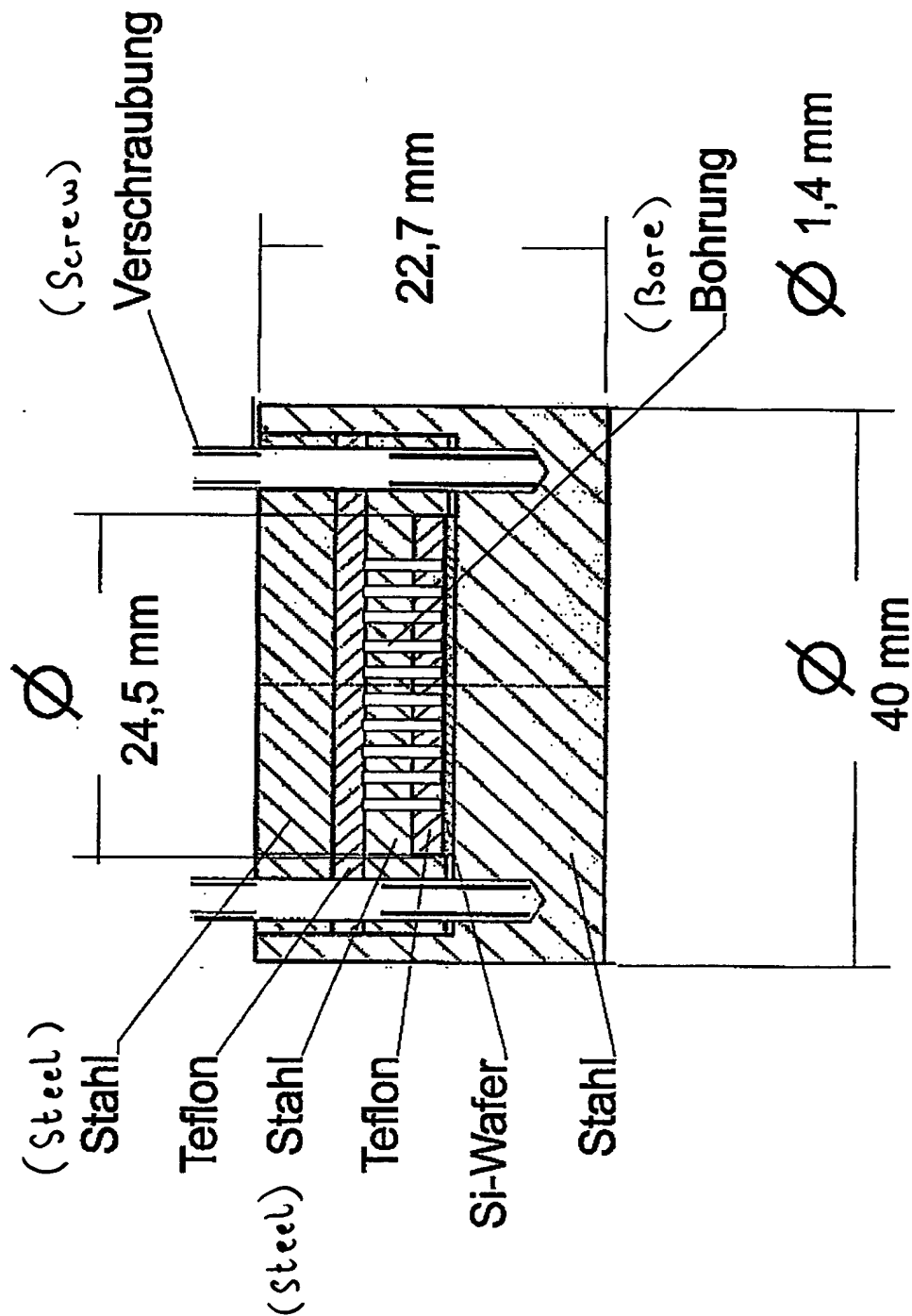


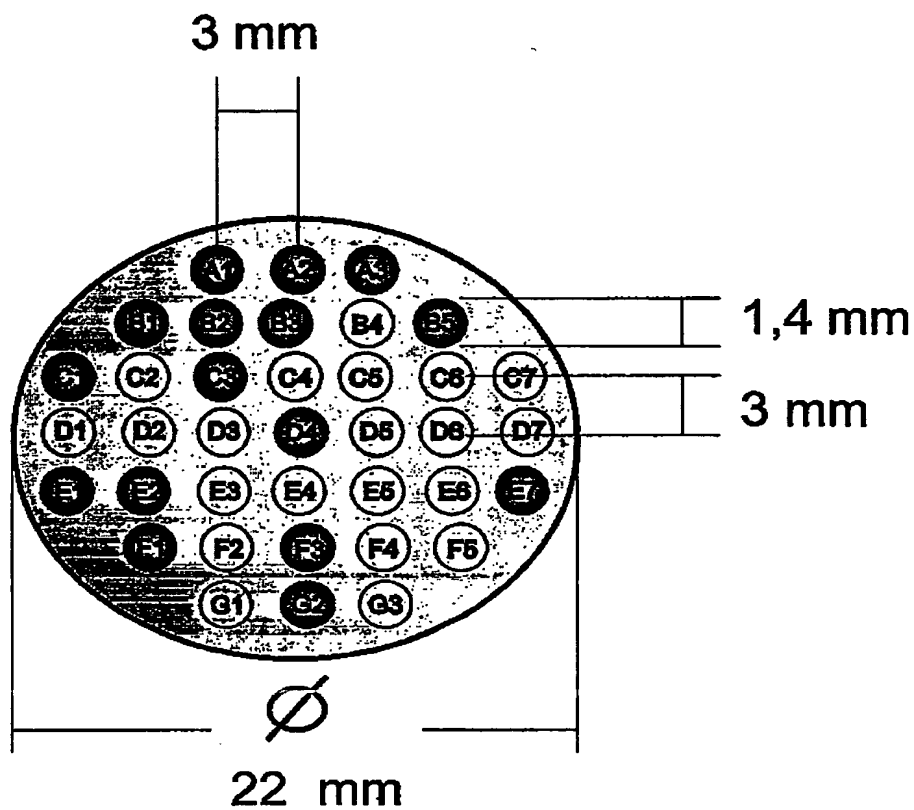
Abbildung 1

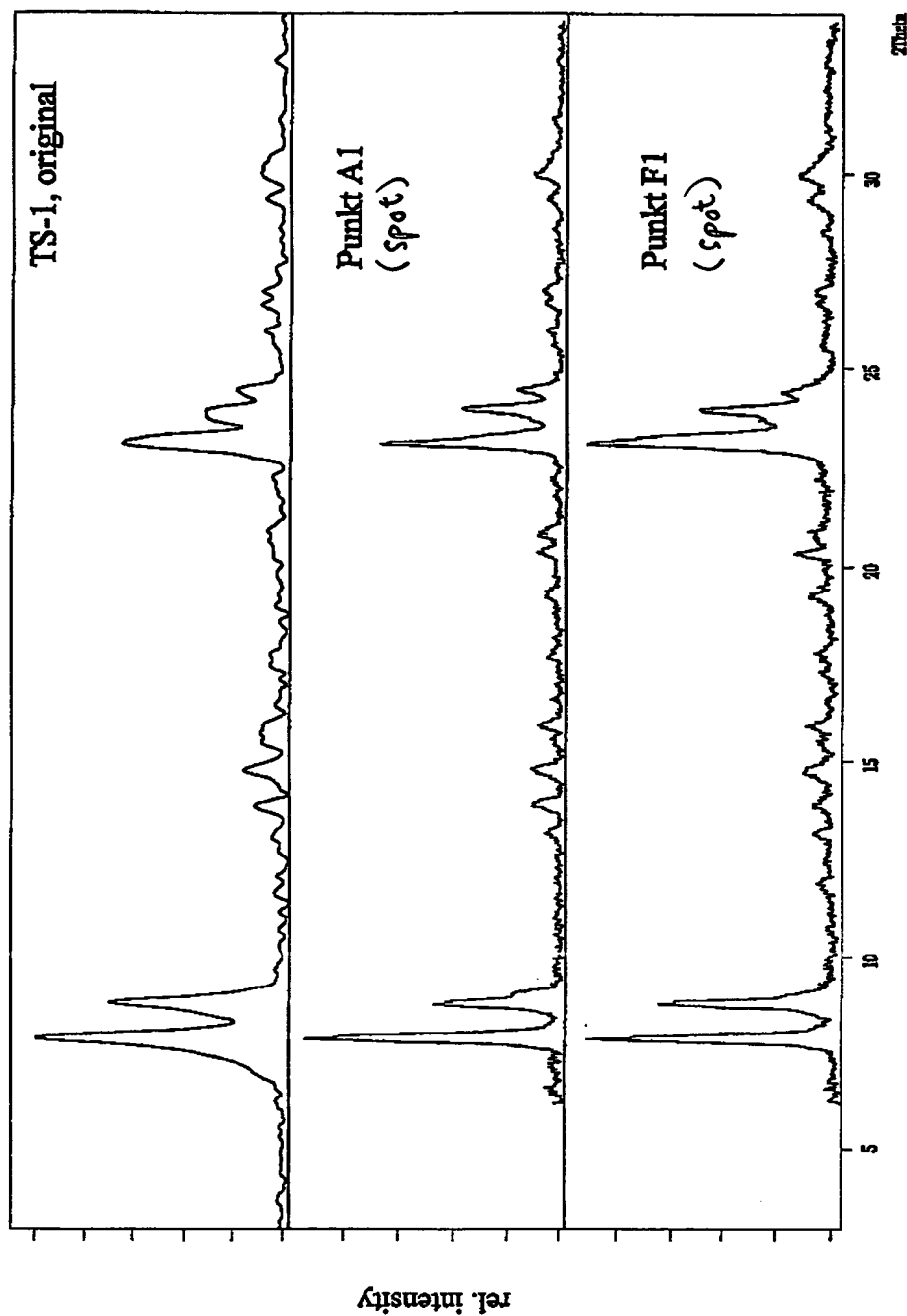
(figure 1)

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Abbildung 2

(figure 2)





(Figure 3)
Abbildung 3